ISSN 1070-3632, Russian Journal of General Chemistry, 2006, Vol. 76, No. 11, pp. 1753–1756. © Pleiades Publishing, Inc., 2006.
Original Russian Text © A.A. Prishchenko, M.V. Livantsov, O.P. Novikova, L.I. Livantsova, D.B. Shpakovskii, E.R. Milaeva, 2006, published in Zhurnal Obshchei Khimii, 2006, Vol. 76, No. 11, pp. 1834–1838.

Synthesis of Phosphorus Derivatives of 2,6-Di-*tert*-butyl-4-methylphenol

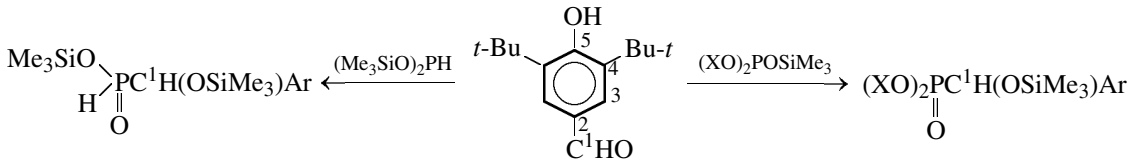
A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, D. B. Shpakovskii, and E. R. Milaeva

Moscow State University,
Vorob'evy Gory, Moscow, 119992 Russia
e-mail: liv@org.chem.msu.su

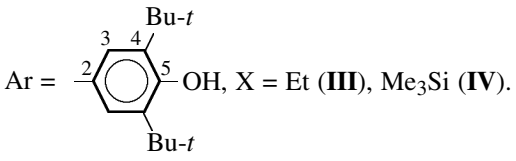
Received July 31, 2006

Abstract — Convenient procedures for the synthesis of 2,6-di-*tert*-butyl-4-methylphenol (ionol) mono-, di- and triphosphorus derivatives, starting from the readily accessible 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde, are proposed, and some properties of the obtained compounds are presented.
DOI: 10.1134/S1070363206110132

Sterically hindered phenols are widely used for preparation of stable phenoxyl radicals and are interesting as biologically active compounds [1]. Phosphorus derivatives of 2,6-di-*tert*-butyl-4-methylphenol (ionol) are effective antioxidants and promising ligands. However, the methods for synthesis of such compounds are rather complicated and require rigid conditions [2–5]. In this work we propose convenient procedures for synthesis of a series of ionol phosphorus derivatives with one, two or three phosphorus-containing groups, starting from the readily accessible 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**I**) prepared by the procedure in [6] and trimethylsilyl P(III) acid esters. We found that the latter add to aldehyde **I** to form new phosphorus-containing sterically hindered phenols. Thus bis(trimethylsiloxy)phosphine and trimethylsilyl phosphites readily add by the carbonyl group of aldehyde **I** in methylene chloride to afford phosphinate **II** or phosphonates **III**, **IV**, respectively, in high yields. Note that under the applied conditions, the sterically hindered hydroxy group of aldehyde **I** is not trimethylsilylated with excess bis(trimethylsiloxy)-phosphine or trimethylsilyl phosphite (cf. [7]).

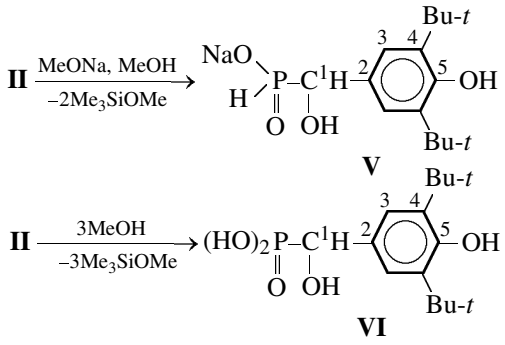


II **I** **III, IV**



Treatment of phosphinate **II** with dilute sodium methoxide in methanol gave sodium phosphinate **V**, and the reaction of phosphonate **IV** with excess methanol gave free phosphonic acid **VI** as white hygroscopic crystals. Under similar conditions, phosphonate **III** does not react with methanol.

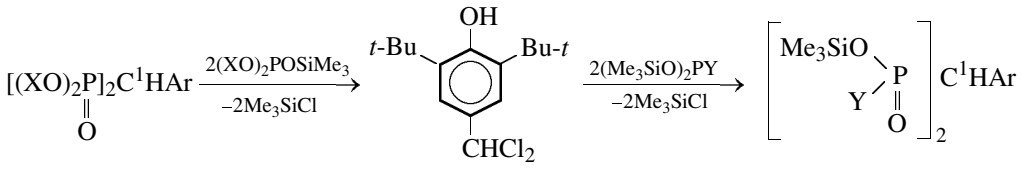
Reactions of trimethylsilyl esters of P(III) with the easily accessible 2,6-di-*tert*-butyl-4-(chloromethyl)-phenol **A** prepared from aldehyde **I** by the procedure in [8] give rise to new methylenediphosphorus compounds which include sterically hindered phenol fragments. Thus, trimethylsilyl phosphites and func-



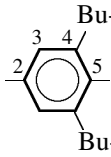
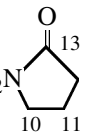
V

VI

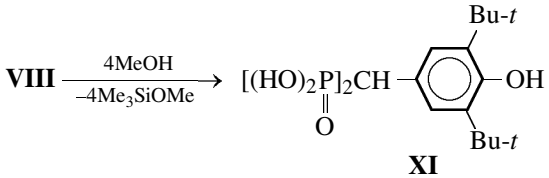
tionally substituted trimethylsilyl phosphonites readily react with chloride **A** in methylene chloride medium by the Arbuzov reaction scheme to form, respectively, bisphosphonates **VII**, **VIII** or bisphosphinates **IX**, **X** in high yields. In these cases, too, the sterically hindered hydroxy group of chloride **A** is not trimethylsilylated with excess trimethylsilyl phosphite or trimethylsilyl phosphonites, that is, the sterically hindered phenolic fragment is preserved (cf. [9]).



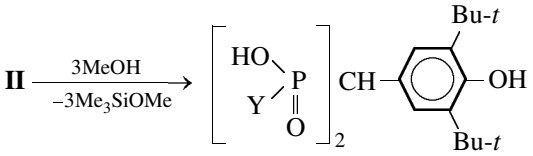
VII, VIII **A** **IX, X**

Ar =  , X = Et (**VII**), Me_3Si (**VIII**); Y = $C^6H_2C^7H_2$  (**IX**),  (**X**).

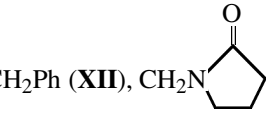
By the reactions of bisphosphonate **VIII** and bisphosphinates **IX**, **X** with excess methanol we also prepared substituted methylenebisphosphorus acids **XI**–**XIII** in high yields. The products are white hydroscopic crystals.



XI



XII, XIII

Y = CH_2CH_2Ph (**XII**),  (**XIII**).

Under mild methanolysis conditions, the phenolic fragments in compounds **VIII**–**X** are preserved, while the hydrolysis of compound **VII** under heating with HCl results in elimination of the *tert*-butyl groups from the phenolic fragment [10]. By the oxidation of diphosphonate **VII** by the procedure in [4] we prepared diphosphorus-substituted methylenequinone **XIV** which was further used to synthesize triphosphorus-containing ionol **XV**. Thus, 1,6-addition of diethyl phosphite to methylenequinone **XIV** proceeds readily in the presence of the sodium hydride reaction initiator and yields 85% of compound **XV** (cf. [5]).

To conclude, we proposed convenient syntheses of new or hardly accessible ionol derivatives of various structures, which are interesting as effective antioxidants, prospective ligands, and biologically active compounds. The structures of compounds **I**–**XV** were confirmed by the ^1H, ^{13}C and ^{31}P NMR spectra which show characteristic signals of the $P_nC^1H_m$ fragments and signals of substituted aromatic fragments (see table). As follows from the NMR data, compounds **II** and **X** are mixtures of two stereoisomers in a 7 : 3 ratio (measured by ^{31}P NMR); in the table, data for the predominating isomer are given first). The methylene proton signals of compounds **IX**, **X**, **XII**, and **XIII** are partially overlapping. The elemental analyses of the synthesized compounds, confirmatory of the proposed compositions, have also been reported in preliminary communications [11].

Physicochemical constants and NMR spectral data (δ, ppm, *J*, Hz) of comopounds **I**–**XV** [a]

Comp. no.	Yield, %	mp, °C	δ(C^1H)	$^2J_{PH}$	δ(C^3H), s	δ(OH), s	δ(C^1)	$^1J_{PC}$	δ(C^2)	$^2J_{PC}$	δ(C^3)	$^3J_{PC}$	δ(C^4), s	δ(C^5), s	δ_P, s
I	80	189	9.87 s	–	7.75	5.90	191.85 s	–	127.68 s	–	128.75 s	–	136.55	159.70	–
II	85	[b]	4.84 d	8	7.13	5.27	73.59 d	119	123.38 s	–	126.13 s	–	135.83	153.71	24.30
			4.72 d	12	7.12	5.27	74.23 d	118	123.88 s	–	125.81 s	–	135.95	153.89	24.65
III	92	102	4.97 d	12	7.19	6.93	71.74 d	170	124.21 s	–	128.45 s	–	138.94	153.91	20.49
IV	85	98	4.81 d	16	7.21	5.16	72.62 d	180	124.17 s	–	128.33 s	–	125.34	153.40	4.93
V	95	159 [c]	4.48 d	8.1	7.16	[d]	73.90 d	105	123.96 s	–	129.70 s	–	139.74	152.55	29.42
VI	97	198 [c]	4.54 d	16	7.17	[d]	71.25 d	159	124.47 s	–	131.08 s	–	138.51	153.75	19.17
VII	90	140	3.62 t	24	7.24	5.45	45.19 t	132	120.12 t	6	127.25 t	6	135.87	153.35	19.39
VIII	89	156	3.40 t	26	7.17	5.16	48.79 t	140	122.89 t	8.5	127.31 t	6	135.70	153.16	0.17
IX	91	119	3.29 t	18	7.14	5.20	49.98 t	78.5	120.98 t	7	127.10 t	6	136.34	153.63	37.96
X	94	71	3.94 t	17	7.40	5.30	50.17 t	78	118.60 t	7	126.25 s	–	136.78	153.70	29.91
			3.94 t	17	7.40	5.30	50.97 t	77	119.52 t	5.5	127.72 s	–	135.99	153.63	29.18
XI	97	201	3.60 t	26	7.22	[d]	45.85 t	126	123.42 t	7.5	127.04 t	5.5	139.87	152.26	18.35
XII	95	202	3.82 t	18	7.36	[d]	49.27 t	75	123.14 t	5.5	127.63 t	6	139.47	153.40	43.20
XIII	96	122	3.64 t	20	7.27	[d]	49.36 t	74	121.57 t	5.5	127.84 s	–	138.76	153.30	35.01
XIV	91	74 [e]	–	–	8.24	–	127.08 t	161	153.61 s	–	130.38 t	15	151.03	186.33	14.01
XV	85	162	–	–	7.89	5.18	57.65 q	116	119.74 q	7	128.81 q	7	134.43	152.79	16.12

[a] PH fragment. ^1H NMR spectrum, δ, ppm (*J*, Hz): compound **II**: 6.91 d ($^1J_{PH}$ 552) and 6.83 d ($^1J_{PH}$ 552); compound **V**: 6.67 d ($^1J_{PH}$ 510.3). ^{13}C NMR spectrum, δ, ppm (*J*, Hz). Compound **IX**: 33.17 d (C^6, $^1J_{PC}$ 96), 28.66 d (C^7, $^2J_{PC}$ 4), 141.29 d (C^8, $^3J_{PC}$ 16); compound **X**, first isomer: 43.61 d (C^9, $^1J_{PC}$ 108), 48.47 s (C^{10}), 17.79 s (C^{11}), 30.00 s (C^{12}), 174.66 d (C^{13}, $^3J_{PC}$ 3); second isomer: 43.50 d (C^9, $^1J_{PC}$ 106), 48.40 s (C^{10}), 17.72 s (C^{11}), 30.00 s (C^{12}), 174.46 s (C^{13}); compound **XII**: 31.59 d (C^6, $^1J_{PC}$ 94), 27.96 d (C^7, $^2J_{PC}$ 3), 142.26 d (C^8, $^3J_{PC}$ 17); compound **XIII**: 42.75 d (C^9, $^1J_{PC}$ 106), 48.08 s (C^{10}), 17.94 s (C^{11}), 30.15 s (C^{12}), 174.31 s (C^{13}). [b] Oily substance. [c] Broad signal. [d] With decomposition. [e] Orange crystals.

EXPERIMENTAL

The ^1H, ^{13}C and ^{31}P NMR spectra were registered on a Bruker Avance-400 instrument (400, 100, and 162 MHz, respectively) in $CDCl_3$ (**I, II, IV, VII–X, XIV**, and **XV**), $(CD_3)_2SO$ (**III, VI, XII**, and **XIII**), or D_2O (**V** and **XI**) against TMS (^1H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were performed under dry argon in water-free solvents. Aldehyde **I**, chloride **A**, and methylenequinone **XIV** were prepared according to the procedures in [6, 8, 4], respectively.

Trimethylsilyl [3,5-di-*tert*-butyl-4-hydroxyphenyl(trimethylsiloxy)methyl]phosphonite (II). 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (**I**), 2.3 g, was added with stirring to a solution of 5.3 g of bis(trimethylsiloxy)phosphine in 30 ml of methylene chloride, cooled to 0°C. The mixture was stirred for 0.5 h, the solvent was then distilled off, and the residue was kept at 40°C in a vacuum (0.5 mm Hg) for 1 h to obtain 3.8 g of phosphinate **II** as a thick oil.

Diethyl [(3,5-di-*tert*-butyl-4-hydroxyphenyl)(trimethylsiloxy)methyl]phosphonate (III). Aldehyde **I**, 3.1 g, was added with stirring to a solution of 6.2 g of diethyl trimethylsilyl phosphite in 30 ml of methylene chloride, cooled to 10°C. The mixture was stirred for 0.5 h, the solvent was then distilled off, the residue was diluted with 20 ml of hexane, and the mixture was cooled to 0°C. The white crystals that dropped were filtered off and kept in vacuum (0.5 mm Hg) for 1 h to obtain 5.4 g of phosphonate **III**. Found, %: C 59.09; H 9.22. $C_{22}H_{41}O_5PSi$. Calculated, %: C 59.43; H 9.29.

Phosphonate **IV** was prepared similarly.

Sodium [(3,5-di-*tert*-butyl-4-hydroxyphenyl)(hydroxy)methyl]phosphinate (V). A solution of 3.8 g of phosphinate **II** in 20 ml of methanol was added with stirring to a solution of 0.46 g of sodium methoxide in 10 ml of methanol. The solvent was then distilled off, and the residue was kept in a vacuum (1 mm Hg) for 1 h to obtain 2.6 g of salt **V**. Found, %: C 55.65; H 7.46. $C_{15}H_{24}NaO_4P$. Calculated, %: C 55.90; H 7.50.

[(3,5-Di-*tert*-butyl-4-hydroxyphenyl)(hydroxy)methyl]phosphonic acid (VI). Phosphonate **IV**,

3.8 g, was added with stirring to 30 ml of methanol cooled to 10°C of. The mixture was heated to boiling, the solvent was distilled off, and the residue was kept in a vacuum (1 mm Hg) for 1 h to obtain 2.2 g of acid **VI**. Found, %: C 56.78; H 7.89. $C_{15}H_{25}O_5P$. Calculated, %: C 56.95; H 7.97.

Acids **XI**–**XIII** were prepared similarly.

Tetraethyl (3,5-di-*tert*-butyl-4-hydroxyphenyl)-methylenebis(diethyl phosphonate) (VII). A solution of 3.7 g of chloride **A** in 15 ml of methylene chloride was added with stirring to a solution of 6.8 g of diethyl trimethylsilyl phosphite in 20 ml of methylene chloride, cooled to 0°C. The mixture was stirred for 0.5 h, heated to boiling, the solvent was distilled off, the residue was diluted with 20 ml of hexane and cooled to 0°C. The white crystals that dropped were filtered off and kept in a vacuum (0.5 mm Hg) for 1 h to obtain 5.7 g of compound **VII** (cf. [3]).

Compounds **VIII**–**X** were prepared similarly.

(3,5-Di-*tert*-butyl-4-hydroxyphenyl)tris(diethoxyphosphinoyl)methane (XV). Diethyl phosphite, 7.5 g, was added with stirring to a mixture of 3.3 g of methylenequinone **XIV** and 0.01 g of sodium hydride. When the mixture decolorized, 30 ml of hexane and 3 ml of water were added. The mixture was stirred for 0.5 h, the organic layer was separated, heated to boiling, and cooled to 10°C. The white crystals that dropped were filtered off and kept in a vacuum (0.5 mm Hg) for 1 h to obtain 3.6 g of compound **XV**. Found, %: C 51.47; H 8.09. $C_{27}H_{51}O_{10}P_3$. Calculated, %: C 51.59; H 8.18.

ACKNOWLEDGMENTS

The work was financially supported by the Russian Foundation for Basic Research (project nos. 05-03-32864 and 06-03-32731).

REFERENCES

1. Nonhebel, D., Tedder, J., and Walton, J., *Radicals,* Cambridge: Cambridge Univ. Press, 1979.
2. Mukmeneva, N.A., Kadyrova, V.Kh., and Zharkova, V.M., *Zh. Obshch. Khim.,* 1992, vol. 62, no. 7, p. 1670; Mukmeneva, N.A., Cherezova, E.N., and Zhukova, R.S., *Zh. Obshch. Khim.,* 1994, vol. 64, no. 6, p. 1049.
3. Gross, H., Seibt, H. and Keitel, I., *J. Prakt. Chem.,* 1975, vol. 317, p. 890.
4. Ismagilov, R.K., Moskva, V.V., and Kopylova, R.Yu., *Zh. Obshch. Khim.,* 1989, vol. 59, no. 7, p. 1686.
5. Gross, H., Ozegowski, S., and Costisella, B., *Phosphorus, Sulfur, Silicon, Relat. Elem.,* 1990, vol. 47, nos. 1–2, p. 7.
6. Coppinger, G.M. and Campbell, T.W., *J. Am. Chem. Soc.,* 1953, vol. 75, no. 3, p. 734.
7. Prishchenko, A.A., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., and Kashulin, I.A., *Zh. Obshch. Khim.,* 2005, vol. 75, no. 10, p. 1748; Prishchenko, A.A., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., and Maryashkin, A.V., *Zh. Obshch. Khim.,* 2005, vol. 75, no. 12, p. 2055.
8. Popov, L.K., Egidis, F.M., and Ershov, V.V., *Izv. Akad. Nauk SSSR., Ser. Khim.,* 1968, no. 4, p. 902.
9. Friedman, S., Kaufman, M.L., and Wender, I., *J. Org. Chem.,* 1962, vol. 27, no. 2, p. 664.
10. Gross, H. and Ozegowski, S., *Phosphorus, Sulfur, Silicon, Relat. Elem.,* 1990, vol. 47, nos. 1–2, p. 1.
11. Prishchenko, A.A., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., Shpakovskii, D.B., and Milaeva, E.R., *Zh. Obshch. Khim.,* 2005, vol. 75, no. 12, p. 2058; Prishchenko, A.A., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., Shpakovskii, D.B., and Milaeva, E.R., *Zh. Obshch. Khim.,* 2006, vol. 76, no. 5, p. 868.